ORIGINAL ARTICLE

The Role of Concurrent Chemo Radiation in Locally Advanced Esophagel Cancer

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ABSTRACT

Objective: To assess the response of cisplatin & 5 flurouracil based concurrent chemo radiation in locally advanced esophageal cancer.

Methods: This descriptive case series study was conducted in the Department of Clinical Oncology LINAR Cancer Hospital Larkana from Januay 2016 to August 2017 ,on histological proven squamous cell carcinoma of esophagus fulfilling inclusion criteria. Excluding cases with carcinoma of cervical esophagus, infiltration of tumor in tracheobronchial tree, distant metastasis. We planned our patients with EBRT have total dose of radiation 50.4Gy in 28 fractions. Inj Cisplatin 75mg/m2 IV D1 & Inj 5-Flurouracil 1000mg/m2 IV D1 to D4 were infused during 1st & 5th week of external beam radiotherapy & 8th & 11th weeks. The response of treatment was assessed four weeks later radiologically on CT scan chest & abdomen with contrast. The data was statistically analyzed.

Results: Majority of patients having age above 40 years. The average age of patients & duration of disease were 46.45 +/- 10.59 years (95%CI: 46.45+/- 10.59) and 3.5 +/-1.17 months (95%CI:3.20 to 3.80) respectively. 27(43.5%) were male & 35(56.5%) were female. The response of treatment was assessed four weeks later radiologically on CT scan chest & abdomen with contrast according to response evaluation criteria in solid tumors (RECIST). Complete response rate was 24.2% and partial response rate was 50%.Progressive disease was observed in 6.5% cases and disease was stable in 19.4% cases.

Conclusion: Con-current pre-operative chemo-radiation for locally advanced esophageal cancer is associated with good clinical response and it is very effective and safe in our setting.

Keywords: - Locally Advanced Esophageal cancer, Chemo radiation, Radiotherapy

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INTRODUCTION:

The esophageal cancer is a highly lethal malignancy with a dismal prognosis. Globally carcinoma of esophagus is 6th most common cancer in mortality rate among various histo-pathologic types of cancer.[1] In 2015 an estimated 16980 people were diagnosed with esophageal cancer in United States. Esophageal cancer is a malignant disease with a wide range of global variation in its incidence.[2]

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Esophageal cancer is 6th common malignant neoplasm reported in Karachi, while 7th most common malignant neoplasm reported in Pakistan[3]. According to KIRAN cancer registry (KCR) report, there were 19559 patients registered from 1st Jan 2000 to 31st Dec 2009 in which 743(3.8%) patients were suffering from carcinoma of esophagus more in males than females.[4]

The overwhelming majority of esophageal cancer may be classified as either squamous cell carcinoma or adenocarcinoma, while less common histologies include adenoid cystic carcinoma, mucoepidermoid carcinoma, small cell carcinoma, lymphoma and leiomyosarcoma.[5] Approximately 60% of these tumors arose in middle third of esophagus, whereas 30% & 10% arose in distal and proximal third of the intrathoracic esophagus respectively. Despite much technical advancement, esophageal cancer still represents a therapeutic challenge. The majority of patients with esophageal cancer are present in the advanced stage i-e III& IV[6].There is dramatic evaluation in treatment of locally advanced esophageal cancer in last 15 years. Surgery remains mainstay of treatment in advanced stage esophageal cancer. Patients of locally advanced stage esophageal cancer who underwent for curative surgery having 03 years survival rate approximately 20% & post surgical mortality rate was 3 to 10% [7].There is emerging role of combined modality approaches since last decade for management of locally advanced stage esophageal cancer.

A land mark trial RTOG -85-01 which addresses combined chemo radiation therapy Inj cisplatin 75 mg/m2 IV D1 of 1st, 5th, 8th& 11th week & Inj 5 Flurouracil 1000 mg/m2 24 hours infusion from D1 to D4 of 1st, 5th, 8th, 11th week with radiotherapy dose of 50.4 Gy was compared with 64 Gy radiotherapy in 32 fractions completed in six to seven weeks[8,9]. In RTOG -85-01 trial patients 05 years overall survival was compared. It was 0% in radiotherapy alone arm versus 26% in chemo radiation arm.[10] 80% of the patients had down staging in tumor and 16%to26% had complete pathological response. The side effects that are observed during radiotherapy of esophageal cancer are usually self limiting and toxicity of chemotherapy are also manageable.

METHODS:

This descriptive prospective case series study was conducted in the Department of Clinical Oncology LINAR cancer Hospital Larkana from January 2016 to August 2017. We have enrolled sixty two patients by non probability sampling, on histological proven squamous cell carcinoma of esophagus staged radiologically T3-T4,No,-1,Mo according to TNM Classification, ECOG performance status 0,1 or 02,normal hematologic profile & normal function of liver and kidney by routine laboratory examination (i-e CBC, LFT,RFT).While exclusion criteria were adenocarcinoma of esophagus, carcinoma of cervical esophagus, carcinoma of gastro esophageal junction, patients with esophageal biopsy of lymphoma, leiomyosarcoma, adeno-cystic carcinoma, small cell carcinoma, infiltrations of tumor into tracheobronchial tree, distant metastasis(i-e liver, adrenal glands). Radiation planning was performed on 2 dimensional external beam radiotherapy techniques. Gross tumor volume and nodal involvement were delineated through CT scan neck, chest with contrast performed for staging purpose.50.4 Gy dose of radiotherapy was delivered in 28 fractions at rate of 1.8 Gy per fraction in two phases. In phase I we delivered external beam radiotherapy through 02 fields anterior & posterior up to 36 Gy, with 05 cm proximal & distal margins to tumor and 03 cm transverse margins for nodal coverage for achieving 95% dose delivery at planning target volume. In phase II external beam radiotherapy was delivered through 03 fields one anterior & two posterior oblique fields with adequate coverage of tumor target volumes through sparing organ at risk i-e lungs, spinal cord & heart to prevent from radiotherapy induced injuries to these critical organs. Inj cisplatin 75 mg/m2 IV D1 of week 1st, 5th,8th & 11th and Inj 5 Flurouracil 1000mg/m2 24 hours IV infusion during 1st, 5th, 8th & 11th weeks were infused. Results were analyzed statistically.

RESULTS

Sixty two patients of locally advanced esophageal cancer included in study. Most of the patients were above 40 year of age. The average age of patients and duration of disease was 46.45±10.59 years (95%CI: 46.45±10.59) and 3.5±1.17 months (95%CI: 3.20 to 3.80) respectively as presented in Table I.

27(43.5%) were male and 35(56.5%) were female Figure I. Dysphagia was the commonest clinical presentation i.e. 37(59.7%) followed by vomiting in 18(29%) and weight loss in 7(11.3%) cases. Stage III-C 34%, stage IIIB 26% and stage

IIB 17% was found in patients Table II. The response of concurrent chemo radiation was assessed in form of radiological response at 04 weeks after completion of treatment according to response evaluation criteria in solid tumors (RECIST) Table III & figure III.

Table I. Descriptive Statistics of Patients (n=62)

Statistics	Age (Years)	Duration of Disease (Months)
Mean+SD	46.45+10.59	3.5+1.17
95% Confidence Interval	43.76 to 49.14	3.20 to 3.80
Median (IQR)	58.5 (16)	3.1 (1)
Maximum	62	7
Minimum	25	2

Table II. Stage of Disease (n=62)

Stage	Percentage
Stage IIB	17%
Stage IIIA	23%
Stage IIIB	26%
Stage IIIC	34%

Table III. Response of Cisplatin and 5-Flurouracil Based Chemo Radiation according to RECIST criteria (n=62)

Radiological	Frequency	Percentage
Complete Response (CR)	15	24.2%
Partial Response (PR)	31	50 %
Progressive Disease (PD)	4	6.5%
Stable Disease (SD)	12	19.4%

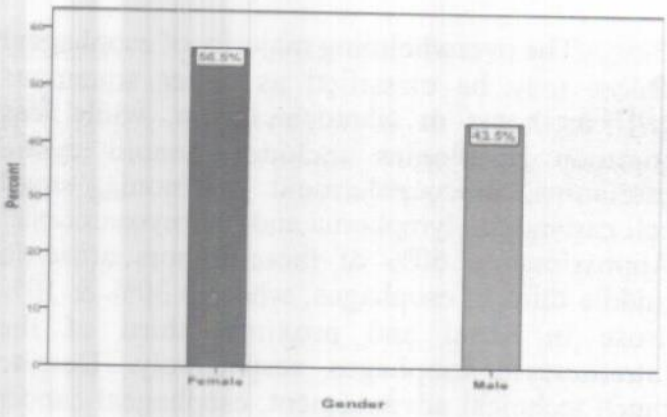

Figure. I: Gender Distribution (n=62)

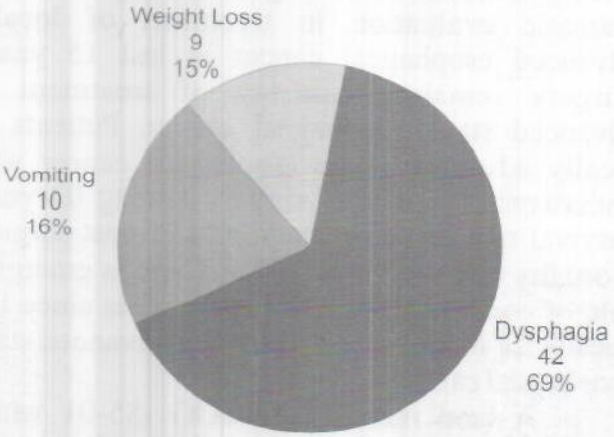

Figure. II: Clinical Presentations)n=62)

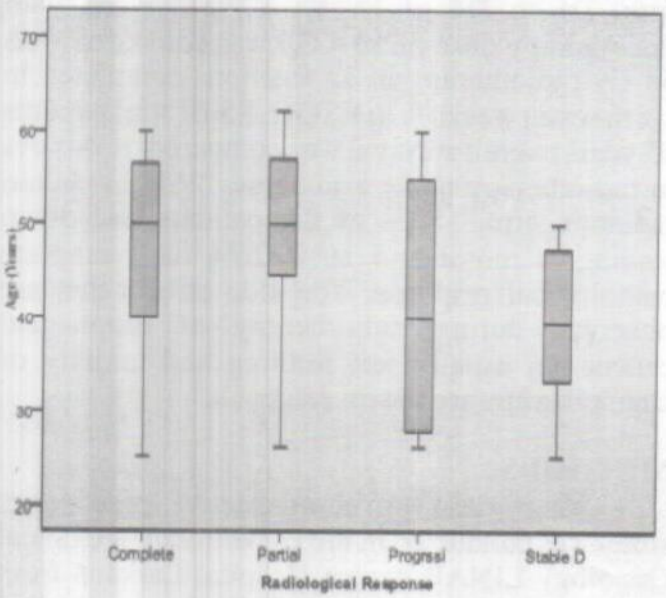

Figure. III: Response of Cisplatin and 5-FU Based Concurrent Chemo Radiation according RECIST criteria

DISCUSSION

Locally advanced esophageal cancer remains a great challenge to surgical oncologist, medical oncologist & radiation oncologist. Esophagectomy has been standard of care, however its role has been challenged due to generally poor outcome following surgical resection alone in locally advanced stage esophageal cancer. Locoregional recurrence is most common mode of failure after surgical resection alone. Neo adjuvant chemotherapy alone use has conflicting results in treatment of esophageal cancer.[11]

Con current chemo radiation was a common mode of treatment between 1988 to 1993 in comparison to surgery alone as management of locally advanced esophageal cancer in united states.[12] Currently in many institutions, primary resection is differed in favor of combined modality therapy with or without esophagectomy. There are no randomized studies comparing surgery alone with radiation alone, and, radiation therapy alone has been usually delivered when lesions are deemed inoperable because of tumor extent or medical contraindications and/or when palliative treatment is indicated. The landmark trial establishing the superiority of concurrent chemo radiation to radiation therapy alone was RTOG 8501. Herskovic et al. [8] reported results of this two-arm trial that treated 60 control patients with radiation alone to a total dose of 64 Gy versus 61 patients with 50 Gy of radiation therapy with concurrent chemotherapy. The chemotherapy protocol consisted of four planned courses of infusion 5-FU and cisplatin. Although less radiation was delivered in the concurrent-therapy arm, the results demonstrated a significant advantage of the combined-modality arm over the radiation-alone arm. The median survival in patients treated by radiation alone was 8.9 months compared with 12.5 months for those treated with combined therapy. The 2-year survival rate with the addition of chemotherapy improved from 10% to 38%, the incidence of local recurrence decreased from 24% to 16%, and the 2-year distant metastases rate decreased from 26% to 12%.

Based on the positive results from RTOG 85-01 trial non surgical treatment for carcinoma of esophagus is combined modality therapy. Collectively these and other trials indicate that radiotherapy alone should be reserved for patients who are medically unfit to receive chemotherapy. Combined modality therapy should be standard of care. It should be noticed that concurrent chemo radiation is an intensive treatment with potentially severe acute side effects. In RTOG-trial 10% have severe acute side effects with combined therapy versus 2% in only radiotherapy group. But with careful attention to nutritional status of patients and their symptoms during treatment and hospitalization during concurrent chemo radiation could keep acute side effects in a manageable state, and we could prescribe full treatment according to protocol. In our study the objectives were to see radiological response with chemo-irradiation. Sixty two patients with thoracic esophageal cancer were included in this study. Most of the patients were above 40 year of age. The average age and duration of disease the patients was 46.45±10.59 years (95%CI: 46.45±10.59) and 3.5±1.17 months (95%CI: 3.20 to 3.80) respectively. Out of 62 cases, 27(43.5%) were male and 35(56.5%) were female. Stage III-C 34%, stage IIIB 26% and stage IIB 17% was commonly seen in patients. The response of concurrent chemo radiation was assessed in form of radiological response at 04th weeks after completion of treatment according to response evaluation criteria in solid tumors (RECIST)[14]. Complete response rate of cisplatin and 5-flurouracil based chemo radiation in patient was 24.2% and partially response rate was 50%. Progressive disease was observed in 6.5% cases and disease was stable in 19.4% cases. In our study, high frequency of clinical down staging could be explained by less accurate methods of clinical staging due to lack availability of endoscopic ultrasonography (EUS) and bronchoscopy to evaluate for the presence of tracheal or carinal invasion, particularly for patients with tumors abutting these structures on computed tomography (CT). Importantly, emerging data suggest that PET can be used to predict response to therapy with PETresponders experiencing significantly improved outcomes compared to no responders. Additionally PET has been used to predict therapeutic response to treatment early in the treatment course. This has led to investigation of early treatment response as measured by PET as a surrogate for therapeutic efficacy and clinical

outcomes[15].

Maria Tessa et al[13] have conducted multi centric retrospective study for response evaluation of con current chemo radiation in locally advanced stage esophageal cancer. This study showed 33% complete response, 53% partial response, 09% stable disease and 1% have progression of disease.

CONCLUSION

Con current pre operative chemo radiation for locally advanced esophageal cancer is associated with good clinical response and it is very effective in our setting. It is relatively safe with acceptable morbidity which favors its use in future. Although the regimen is somewhat toxic, but local control rate was high.We recommend that con current chemo radiation should be used for locally advanced esophageal cancer as morbidity & mortality can be reduced.

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